UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,957	01/26/2004	James McSwiggen	02-742-O (400.144)	9923

20306 7590 11/01/2006

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,957	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006 and 08 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,14-21,30 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,14-21,30 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *August 8, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Blast 2 Sequence Results*.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed June 21, 2006 and Applicant's Supplemental Amendment and Remarks filed August 8, 2006.

Claims 2, 4-13, 22-29, 31, and 32 have been canceled.

Claims 1, 3, 14-21, 30, and 33 have been amended.

Claims 1, 3, 14-21, 30, and 33 are pending in the instant application.

Claims 1, 3, 14-21, 30, and 33 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statement filed August 8, 2006 is acknowledged. It is noted that the Examiner has only considered the Abstract of Documents 1 and 3-6. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Priority

It is noted that in the previous Office Action mailed February 21, 2006, the instant application was afforded priority to September 16, 2003, which is the filing date of the parent application 10/665,255, because support for the terms, "about 19 to about 21

base pairs" or "about 21 nucleotides" was not found in any of the later filed parent applications for which Applicants claim benefit. It is acknowledged that Applicants have amended the claims to remove the terms, "about 19 to about 21 base pairs" or "about 21 nucleotides".

It is further noted the instant claims have been amended and are currently drawn to a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence corresponding to (comprising) SEQ ID NO:474. The Examiner would like to point out that Applicants contend that SEQ ID NO:474 represents GenBank entry NM_003376 as disclosed in Tables I and II of the instant specification at pages 150-157 (see Applicant's Remarks filed June 21, 2006 at page 8 of 21, second full paragraph). At the outset, it is noted that the sequence of GenBank Accession Number NM_003376 contains thymine residues, where SEQ ID NO:474 of the instant application has substituted the thymine residues with uracil residues.

The instant application claims priority to a laundry list of U.S. Provisional Applications and pending U.S. Patent Applications, including Provisional Applications 60/358,580, 60/363,124, and 60/386,782, filed February 20, 2002, March 11, 2002, and June 6, 2002, respectively. Due to the voluminous nature and number of the applications to which priority is claimed, Applicant are requested to point out with particularity where such support for the instantly claimed invention may be found in one or more of the prior filed applications to which benefit is claimed, since such support is not readily apparent in the priority documents.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Now then, referring to Provisional Application 60/358,580, it is noted that the Examiner cannot find support for SEQ ID NO:474 or GenBank Accession Number NM_003376. In fact, neither SEQ ID NO:474 nor GenBank Accession Number NM_003376 are even recited in Provisional Application 60/358,580.

Next, referring to Provisional Application 60/363,124, Applicants do contend that support for a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence comprising SEQ ID NO:474 can be found at page 18, lines 1-5 and page 389. When reviewing the nucleotide sequence of GenBank Accession Number NM_003376 (submitted as Document No. 160 on the information disclosure statement filed July 22, 2004), it is immediately noticed that this sequence is 1723 nucleobases in length. Comparing this sequence to SEQ ID NO:474 of the instant specification, it is noted that SEQ ID NO:474 is only 649 nucleobases in length. Given the fact that GenBank Accession Number NM_003376 and SEQ ID NO:474 of the instant invention appear to be different sequences, with very different lengths, it does not appear that Provisional Application 60/363,124 has support for a chemically

modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence corresponding to (comprising) SEQ ID NO:474 as instantly claimed.

Next then, referring to Provisional Application 60/386,782, it is noted that the Examiner cannot find support for SEQ ID NO:474 or GenBank Accession Number NM_003376. In fact, neither SEQ ID NO:474 nor GenBank Accession Number NM_003376 are even recited in Provisional Application 60/386,782.

In summary, Applicants claim priority to a number of parent applications, however, none of the parent applications appear to have support for a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence corresponding to (comprising) SEQ ID NO:474 as instantly claimed. In this regard, the instant claims have been afforded priority to the filing date of the instant application, which is January 26, 2004.

Claim Objections

In the previous Office Action mailed February 21, 2006, claims 18 and 31 were objected to because claim 18 was missing a period at the end of the claim and claim 31 contained a typographical error. **This objection is withdrawn** against claim 18 in view of Applicant's Amendment filed June 21, 2006. Specifically, the Examiner is withdrawing this objection in view of Applicant's Amendment to the claim to add a period

at the end of the claim. **This objection is moot** against claim 31 in view of Applicant's Amendment filed June 21, 2006 to cancel claim 18.

Double Patenting

In the previous Office Action mailed February 21, 2006, claims 1-33 were provisionally rejected under the judicially created doctrine of double patenting over claims 1-30 of copending Application No. US Publication No. 20040209832. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed February 21, 2006.

Response to Arguments

In response to this rejection, Applicants state that they will consider filing a terminal disclaimer upon allowance of the pending claims. The Examiner acknowledges Applicant's consideration.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed February 21, 2006, claims 1-33 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for written description. **This rejection is moot** against claims 2, 4-13, 22-29, 31, and 32 in view of Applicant's Amendment filed June 21, 2006 to cancel these claims. **This rejection is withdrawn** against claims 1, 3, 14-21, 30, and 33 in view of Applicant's Amendment filed June 21, 2006. Specifically, the Examiner is

withdrawing this rejection in view of Applicant's Amendments to the claims to recite, "SEQ ID NO:474".

Claim Rejections - 35 USC § 102

In the previous Office Action mailed February 21, 2006, claims 1, 3-9, 23, and 31-33 were rejected under 35 U.S.C. 102(a) as being anticipated by Reich et al. **This rejection is moot** against claims 4-9, 23, 31, and 32 in view of Applicant's Amendment filed June 21, 2006 to cancel these claims. **This rejection is withdrawn** against claims 1, 3, and 33 in view of Applicant's Amendment filed June 21, 2006. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendments to the claims to recite that the siRNA molecules are chemically modified with 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides. It is noted that Reich et al. do not teach siRNA molecules targeting VEGF that are chemically modified with 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed February 21, 2006, claims 1-33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Reich et al. (Molecular Vision, 2003 Vol. 9:210-216, Applicant's Document No. 256 on the information disclosure statement filed July 22, 2004), in view of Parrish et al. (Molecular Cell, Vol. 6, pp. 1077-1087, 2000, Applicant's Document No. 246 on the information disclosure statement filed July 22, 2004), Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pp.

6877-6888, 2001, Applicant's Document Number 114 on the information disclosure statement filed July 22, 2004), Cook et al. (US 5,587,471), and Schmidt et al. (Nucleic Acids Research, 1996, Vol. 24, No. 4, pages 573-581). **This rejection is moot** against claims 2, 4-13, 22-29, 31, and 32 in view of Applicant's Amendment filed June 21, 2006 to cancel these claims. **This rejection is withdrawn** against claims 1, 3, 14-21, 30, and 33 in view of Applicant's Amendment filed June 21, 2006. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendments to the claims which are currently drawn to a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence corresponding to (comprising) SEQ ID NO:474. It is noted that the combination of Reich et al., Parrish et al., Elbashir et al., Cook et al., and Schmidt et al. does not render the instant claims obvious.

Applicant's Amendment necessitated the new grounds of rejection presented below:

Specification

The amendment filed June 21, 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: In the Amendment filed June 21, 2006, Applicants have submitted a new sequence listing in which SEQ ID NO:474 has been added. Applicants contend that SEQ ID NO:474

represents GenBank entry NM_003376 as disclosed in Tables I and II of the instant specification (see Applicant's Remarks filed June 21, 2006 at page 8 of 21, second full paragraph). It is noted that the sequence of GenBank entry NM_003376 was submitted and made of record as Document No. 160 on the information disclosure statement filed July 22, 2004. Comparing GenBank entry NM_003376 with SEQ ID NO:474 of the instant application, it is noted that the sequence of the Accession Number contains thymine residues, where SEQ ID NO:474 has substituted the thymine residues with uracil residues. It is also apparent that GenBank Accession Number NM_003376 is 1723 nucleotides in length, while SEQ ID NO:474 of the instant invention is only 649 nucleotides in length.

In summary, it is quite evident that GenBank Accession Number NM_003376 and newly submitted sequence SEQ ID NO:474 are not the same sequence since they aren't the same length and one is a DNA sequence, while the other is a RNA sequence. In this regard, SEQ ID NO:474 appears to be new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites the limitation, "wherein the fragment". There is insufficient antecedent basis for this limitation in the claim because claim 1, from which claim 37 depends never recites the term, "fragment". Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 14-21, 30, and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims are drawn to a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence corresponding to (comprising) SEQ ID NO:474. It is noted that SEQ ID NO:474 was added to the sequence listing in the Amendment filed June 21, 2006. The Examiner would like to point out that Applicants contend that SEQ ID NO:474 represents GenBank entry

NM_003376 as disclosed in Tables I and II of the instant specification at pages 150-157 (see Applicant's Remarks filed June 21, 2006 at page 8 of 21, second full paragraph). However, when comparing the sequence of GenBank Accession Number NM_003376 (submitted as Document No. 160 on the information disclosure statement filed July 22, 2004) with SEQ ID NO:474, it appears that the two sequences are not the same since SEQ ID NO:474 is 649 nucleobases, while GenBank Accession Number NM_003376 is 1723 nucleotides. Furthermore, it is immediately noticed that the sequence of GenBank Accession Number NM_003376 contains thymine residues, where SEQ ID NO:474 of the instant application has substituted the thymine residues with uracil residues.

In summary, it is quite evident that GenBank Accession Number NM_003376 and newly submitted sequence SEQ ID NO:474 are not the same sequence since they aren't the same length and one is a DNA sequence, while the other is a RNA sequence. In this regard, SEQ ID NO:474 appears to be new matter. In this regard, SEQ ID NO:474 appears to be new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 14-21, 30, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession Number NM_003376 (Applicant's Document No. 160 on Applicant's information disclosure statement filed July 22, 2004), in view of Reich et al. (Molecular Vision, 2003 Vol. 9:210-216, Applicant's Document No. 256 on the information disclosure statement filed July 22, 2004), Elbashir et al. (EMBO Journal, 2001 Vol. 20:6877-6888, Applicant's Document No. 114 on the information disclosure statement filed July 22, 2004), Matulic-Adamic et al. (US Patent No. 5,998,203), and Parrish et al. (Applicant's Document No. 246 on the information disclosure statement filed July 22, 2004).

Applicant is reminded that the instant application has been afforded priority to the filing date of the instant application, which is January 26, 2004. For further explanation, see the discussion above under the heading "Priority".

Claim 1 is drawn to a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence corresponding to (comprising) SEQ ID NO:474, wherein said siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide. Clams 3, 14-21, 30, and 33 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein said siRNA molecules comprise ribonucleotides; wherein one or more purine or pyrimidine nucleotides are present on the sense strand; wherein the purine nucleotide is a 2'-deoxy purine and the pyrimidine nucleotide is a 2'-deoxy-2'-fluoro pyrimidine nucleotide; wherein the sense strand comprises a terminal cap moiety at the 5' or 3' end, or both;

wherein said terminal cap moiety is an inverted deoxy abasic moiety; wherein the antisense strand comprises 2'-deoxy-2'-fluoro pyrimidine nucleotide; wherein the purine nucleotide on the antisense strand is a 2'-methyl purine nucleotide or a 2'-deoxy purine nucleotide; wherein the antisense strand comprises a phosphororthioate internucleotide linkage at the 3' end of the antisense strand; wherein the 5'-end of the antisense strand includes a terminal phosphate group; and a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a vascular endothelial growth factor (VEGF) nucleotide sequence comprising SEQ ID NO:474, wherein said siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide in a pharmaceutically acceptable carrier or diluent.

GenBank Accession Number NM_003376 teaches the sequence of a human vascular endothelial growth factor (VEGF). It is noted that GenBank Accession Number NM_003376 comprises SEQ ID NO:474 of the instant invention (see attached Blast 2 Sequence results of the sequence alignment of SEQ ID NO:474 with GenBank Accession Number NM_003376, where Query is SEQ ID NO:474 and Sbjct is GenBank Accession Number NM_003376).

GenBank Accession Number NM_003376 does not teach a short interfering ribonucleic acid (siRNA) molecule that is complementary to a VEGF.

Reich et al. teach specific siRNA nucleic acid inhibitors of human VEGF gene expression. Reich et al. teach siRNA targeting human VEGF effectively inhibits ocular neovascularization in a mouse model (see Abstract). Reich et al. teach siRNA duplexes consisting of a sense and antisense strand targeted to human VEGF (see page 211,

first column, first paragraph). Reich et al. also teach RNA interference significantly diminishes levels of human VEGF protein expression (see Figure 3).

Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand (see Abstract). Elbashir et al. teach modification of the internal nucleotides with 2'-deoxy or 2'-O-methyl modifications (see Abstract and Figure 4). Elbashir et al. teach that duplexes 21 nucleotides in length with 2 nt 3' overhangs were the most efficient triggers of sequence-specific mRNA degradation. Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see Figures 7 and 8). Elbashir et al. teach that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures (see Abstract). The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3'-phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach

2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach chemically synthesized double stranded siRNA molecules comprising various modifications in the sense or antisense strand, including 2'-deoxy-2'-fluoro modifications (see Figure 5). One or both strands comprise modifications. Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the RNA interference process (see Summary).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a chemically modified siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a VEGF nucleotide sequence corresponding to (comprising) SEQ ID NO:474 using the sequence taught by GenBank Accession Number NM_003376, the motivation of Reich et al., and following the methods of Elbashir et al., Matulic-Adamic et al., Parrish et al. It would have been obvious to have the siRNA comprised in a pharmaceutically acceptable carrier or diluent using the teachings and motivation of Reich et al.

It would have been obvious to one of ordinary skill in the art at the time of filing to incorporate at least one 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modification into a chemically synthesized siRNA molecule complementary to a VEGF corresponding to SEQ ID NO:474, since Elbashir et al., Matulic-Adamic et al., and Parrish et al. taught

various modifications have been incorporated into double stranded nucleic acids to facilitate uptake of the nucleotide. It would have been obvious to incorporate a terminal cap moiety on one of the ends of the sense strand since Matulic-Adamic et al. taught such modifications protect the nucleic acid from exonuclease degradation. It would have been obvious to incorporate a phosphororthioate internucleotide linkage at the 3' end of the antisense strand or a terminal phosphate group at 5'-end of the antisense strand since either Elbashir et al., Matulic-Adamic et al., and/or Parrish et al. teach such modifications protein the nucleic acid from nuclease attack.

One would have been motivated to incorporate at least one 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications into a chemically synthesized siRNA molecule complementary to a VEGF corresponding to SEQ ID NO:474 since these modifications were known in the art to add benefits to double stranded nucleic acids such as protection from exonuclease degradation and improve uptake of the nucleic acid, as taught by Elbashir et al., Matulic-Adamic et al., Parrish et al. It was well known in the art at the time of filing to incorporate two or more modifications, including 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications, into oligonucleotides, as evidenced by Elbashir et al., Matulic-Adamic et al., and Parrish et al. Elbashir et al. had demonstrated both 2'-deoxy and 2'-O-methyl modifications of double stranded oligonucleotides at the time the invention was made. Matulic-Adamic et al. taught double stranded oligonucleotides comprising more than one specific type of modification. Additionally, Parrish et al. teach various modifications to double stranded duplexes and teach that different modifications are tolerated at different locations of the duplex. Elbashir et al. and Parrish et al.

demonstrate the routine nature of testing various chemical modifications for optimization and stabilization of a double stranded duplex. The cited art demonstrates that the specific modifications were extensively described in the art. One of skill in the art would be motivated to test modifications that are known to benefit oligonucleotide delivery and apply each of them to a double stranded nucleic acid molecule in order to optimize delivery of the nucleic acid. One of skill in the art would be motivated to have the siRNA comprised in a pharmaceutically acceptable carrier or diluent to facilitate its delivery *in vitro* or *in vivo*.

There would be a reasonable expectation of success to apply each of the claimed modifications to the siRNA molecules taught by Reich et al. because the chemistry was well known to one of ordinary skill in the art at the time the invention was made (see Elbashir et al., Parrish et al., and Matulic-Adamic et al.) and merely selecting combinations of such modifications is considered a design choice. Modifications of double stranded ribonucleotides was known to be successful in the art at the time the invention was made and therefore one would reasonably expect for such modifications to benefit the siRNA as instantly claimed.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
October 16. 2006

SEAN McGARRY
PRIMARY EXAMINER
1635

Blast 2 Sequences results

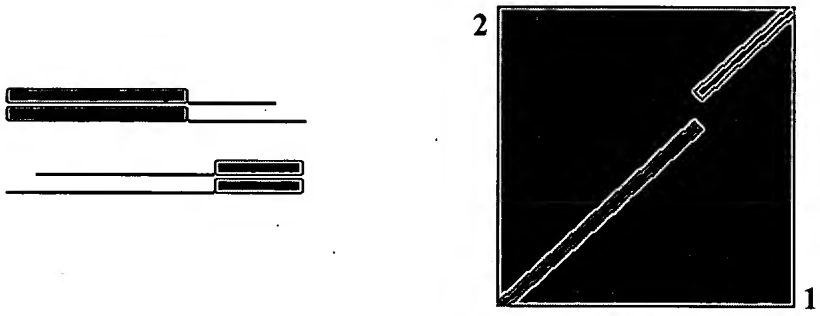
PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.14 [May-07-2006]

Match: 1 Mismatch: -2 gap open: 5 gap extension: 2
x_dropoff: 50 expect: 10.000 wordsize: 11 Filter ☑ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

Sequence 1: lcl|1_seq_1
Length = 649 (1 .. 649)

Sequence 2: lcl|2_seq_2
Length = 721 (1 .. 721)

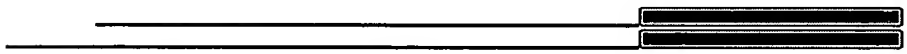


NOTE:Bitscore and expect value are calculated based on the size of the nr database.

NOTE:If protein translation is reversed, please repeat the search with reverse strand of the query sequence.

```
 Score =  842 bits (438),  Expect = 0.0
 Identities = 438/438 (100%), Gaps = 0/438 (0%)
 Strand=Plus/Plus

Query  1    TCGGGCCTCCGAAACCATGAACTTTCTGCTGTCTTGGGTGCATTGGAGCCTTGCCTTGCT  60
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  1    TCGGGCCTCCGAAACCATGAACTTTCTGCTGTCTTGGGTGCATTGGAGCCTTGCCTTGCT  60

Query  61   GCTCTACCTCCACCATGCCAAGTGGTCCCAGGCTGCACCCATGGCAGAAGGAGGAGGGCA  120
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  61   GCTCTACCTCCACCATGCCAAGTGGTCCCAGGCTGCACCCATGGCAGAAGGAGGAGGGCA  120

Query  121  GAATCATCACGAAGTGGTGAAGTTCATGGATGTCTATCAGCGCAGCTACTGCCATCCAAT  180
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
```

```
Sbjct  121  GAATCATCACGAAGTGGTGAAGTTCATGGATGTCTATCAGCGCAGCTACTGCCATCCAAT  180

Query  181  CGAGACCCTGGTGGACATCTTCCAGGAGTACCCTGATGAGATCGAGTACATCTTCAAGCC  240
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  181  CGAGACCCTGGTGGACATCTTCCAGGAGTACCCTGATGAGATCGAGTACATCTTCAAGCC  240

Query  241  ATCCTGTGTGCCCCTGATGCGATGCGGGGGCTGCTGCAATGACGAGGGCCTGGAGTGTGT  300
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  241  ATCCTGTGTGCCCCTGATGCGATGCGGGGGCTGCTGCAATGACGAGGGCCTGGAGTGTGT  300

Query  301  GCCCACTGAGGAGTCCAACATCACCATGCAGATTATGCGGATCAAACCTCACCAAGGCCA  360
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  301  GCCCACTGAGGAGTCCAACATCACCATGCAGATTATGCGGATCAAACCTCACCAAGGCCA  360

Query  361  GCACATAGGAGAGATGAGCTTCCTACAGCACAACAAATGTGAATGCAGACCAAAGAAAGA  420
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  361  GCACATAGGAGAGATGAGCTTCCTACAGCACAACAAATGTGAATGCAGACCAAAGAAAGA  420

Query  421  TAGAGCAAGACAAGAAAA  438
            ||||||||||||||||||
Sbjct  421  TAGAGCAAGACAAGAAAA  438
```



```
 Score =  400 bits (208),  Expect = 3e-108
 Identities = 210/211 (99%), Gaps = 0/211 (0%)
 Strand=Plus/Plus

Query  439  TCCCTGTGGGCCTTGCTCAGAGCGGAGAAAGCATTTGTTTGTACAAGATCCGCAGACGTG  498
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  511  TCCCTGTGGGCCTTGCTCAGAGCGGAGAAAGCATTTGTTTGTACAAGATCCGCAGACGTG  570

Query  499  TAAATGTTCCTGCAAAAACACAGACTCGCGTTGCAAGGCGAGGCAGCTTGAGTTAAACGA  558
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  571  TAAATGTTCCTGCAAAAACACAGACTCGCGTTGCAAGGCGAGGCAGCTTGAGTTAAACGA  630

Query  559  ACGTACTTGCAGATGTGACAAGCCGAGGCGGTGAGCCGGGCAGGAGGAAGGAGCCTCCCT  618
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  631  ACGTACTTGCAGATGTGACAAGCCGAGGCGGTGAGCCGGGCAGGAGGAAGGAGCCTCCCT  690

Query  619  CAGCGTTTCGGGAACCAGATCTCTCACCAGG  649
            ||| ||||||||||||||||||||||||||||
Sbjct  691  CAGGGTTTCGGGAACCAGATCTCTCACCAGG  721


CPU time:    0.02 user secs.      0.01 sys. secs          0.03 total secs.

Lambda     K      H
    1.33    0.621     1.12

Gapped
Lambda     K      H
    1.33    0.621     1.12
```

```
Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 164
Number of extensions: 2
Number of successful extensions: 2
Number of sequences better than 10.0: 1
Number of HSP's gapped: 2
Number of HSP's successfully gapped: 2
Length of query: 649
Length of database: 18,201,043,862
Length adjustment: 26
Effective length of query: 623
Effective length of database: 18,201,043,836
Effective search space: 11339250309828
Effective search space used: 11339250309828
X1: 11 (21.1 bits)
X2: 26 (50.0 bits)
X3: 26 (50.0 bits)
S1: 12 (23.8 bits)
S2: 21 (41.1 bits)
```